Proceedings of the Nutrition Society (2007), **66**, 321–330 DOI:10.1017/S0029665107005587

The Annual Meeting of the Nutrition Society and the British Association for Parenteral and Enteral Nutrition was held at the Hilton Brighton Metropole, Brighton on 1–2 November 2006

Symposium on 'Eating, illness and the gut: is there disorder in the house?'

Signals generating anorexia during acute illness

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Anorexia is part of the body's acute-phase response to illness. Microbial products such as lipopolysaccharides (LPS), which are also commonly used to model acute illness, trigger the acute-phase response and cause anorexia mainly through pro-inflammatory cytokines. LPS stimulate cytokine production through the cell-surface structural molecule CD14 and toll-like receptor-4. Cytokines ultimately change neural activity in brain areas controlling food intake and energy balance. The blood–brain barrier endothelial cells (BBB EC) are an important site of cytokine action in this context. BBB EC and perivascular cells (microglia and macrophages) form a complex regulatory interface that modulates neuronal activity by the release of messengers (e.g. PG, NO) in response to peripheral challenges. Serotonergic neurons originating in the raphe nuclei and glucagon-like peptide-1-expressing neurons in the hindbrain may be among the targets of these messengers, because serotonin (5-HT), acting through the 5-HT_{2C} receptor, and glucagon-like peptide-1 have recently emerged as neurochemical mediators of LPS anorexia. The central melanocortin system, which is a downstream target of serotonergic neurons, also appears to be involved in mediation of LPS anorexia. Interestingly, LPS also reduce orexin expression and the activity of orexin neurons in the lateral hypothalamic area of fasted mice. As the eating-stimulatory properties of orexin are apparently related to arousal, the inhibitory effect of LPS on orexin neurons might be involved in LPS-induced inactivity and anorexia. In summary, the immune signalling pathways of LPS-induced, and presumably acute illness-induced, anorexia converge on central neural signalling systems that control food intake and energy balance in healthy individuals.

Lipopolysaccharides: Food intake: Acute-phase response: Cytokines

Acute infections and other immune challenges trigger a generalized host defence reaction (acute-phase response) that comprises several physiological and behavioural changes including anorexia (for example, see Hart, 1988). The anorexia occurs largely independently of other acute-phase response phenomena such as fever, lethargy or metabolic changes (for review, see Langhans, 2000) and appears to be beneficial for the host initially (for example, see Murray & Murray, 1979), but becomes deleterious over time. The present article reviews the signals that cause anorexia during acute illness. Most of the pertinent knowledge is derived from studies using lipopolysaccharides (LPS), the Gram-negative bacterial cell-wall constituents that are extensively used to model microbial infections.

The model of lipopolysaccharide-induced anorexia

General features

LPS are powerful stimuli of innate immune responses because they have no structural homologue in mammalian organisms (Beutler, 2000). They are released during bacteriolysis or during periods of rapid bacterial proliferation (Rietschel *et al*. 1998). LPS administration triggers a profound pro-inflammatory cytokine response (Abram *et al*. 2000) and, hence, mimics many features of the acute-phase response including the anorexia. LPS have been shown to induce taste aversions in different experimental situations (Langhans *et al*. 1991; Weingarten *et al*. 1993), and conditioning may contribute to LPS anorexia under conditions that favour associative learning (Weingarten

Abbreviations: BBB, blood–brain barrier; EC, endothelial cells; CNTF, ciliary neurotrophic factor; 5-HT, serotonin; IFN-γ, interferon-γ; LPS, lipopolysaccharides; MC*n*-R, melanocortin receptors, where *n* is 3 or 4; TLR, toll-like receptor.

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et al. 1993; Exton *et al*. 1995). However, such learned effects do not appear to play a major role in the anorectic response to LPS under normal circumstances, i.e. when the illness is not associated with a novel diet (Weingarten *et al*. 1993). Fasting attenuates the feeding-inhibitory effect of LPS (Gautron *et al*. 2005), which may be related to the presumed lowering of the body-weight set point by inflammatory mechanisms (Lennie, 1998). While the exact mechanism(s) of this phenomenon are unknown, energy restriction apparently attenuates the stimulatory effect of LPS on macrophage cytokine production (Vega *et al*. 2004) and hypothalamic paraventricular nucleus activation (as evidenced by a reduction in LPS-induced *c-fos* expression; Gautron *et al*. 2005), both of which might curb anorexia in response to LPS. It is also interesting that LPS induces a stronger inhibition of feeding in females than in males (Geary *et al*. 2004), a gender difference mainly related to oestrogen (Geary, 2001; Geary *et al*. 2004). While it is generally accepted that LPS induce anorexia by stimulating the production of cytokines that then act on the brain to inhibit feeding, there are several open questions, including: (1) where and in which cells the stimulation of cytokine production occurs; (2) which brain areas and neurochemicals mediate the resulting behavioural response.

Lipopolysaccharide receptor mechanisms

LPS trigger biological responses by LPS-binding protein-mediated binding to the cell-surface glycoprotein CD14 (Schutt *et al*. 1999), which is present on many immune cells as well as on endothelial cells (EC). Furthermore, in cells devoid of CD14 the circulating soluble form of CD14 can replace membrane-bound CD14 (Akira, 2000). LPS, CD14, the myeloid differentiation protein 2 and the toll-like receptor (TLR)-4, which is the 'true' LPS receptor (Akira, 2000; Beutler, 2000), form the LPS receptor complex. TLR are a family of transmembrane proteins that mainly act as receptors for microbial substances (Akira, 2000; Beutler, 2000). It has been shown that CD14 and TLR4, but not TLR2, are essential for the full expression of LPS anorexia (von Meyenburg *et al*. 2004). LPS activation of TLR4 leads to recruitment of the myeloid adapter protein MyD88, which forms a complex with the Ser/Thr kinase IL-1 receptor-associated kinase that interacts with TNF receptor-activated factor 6. This process activates the transcription factors NF-κB and activating protein-1 (Beutler, 2002) and ultimately triggers the production of pro-inflammatory cytokines, prostanoids and other downstream mediators of LPS effects. The intracellular pathways of LPS and cytokine signalling overlap and have been extensively investigated. The absence of MyD88 signalling has recently been shown to completely eliminate anorexia in response to either LPS or IL-1β (Ogimoto *et al*. 2006). Interference with NF-κB production has also been shown to block the feeding-inhibitory effect of IL-1β (Nadjar *et al*. 2005) and is the most likely mechanism by which genetic lack of PPARβ, administration of phosphodiesterase inhibitors such as pentoxifylline (Porter *et al*. 2000) and some other pharmacological interventions antagonize the feeding-inhibitory effect of LPS (for review, see Langhans, 2004). The neural mechanism(s) that mediate these effects, however, have not yet been determined. In summary, various experimental manipulations that interfere with TLR4 signalling and, hence, pro-inflammatory cytokine production, antagonize the feeding-inhibitory effect of LPS in animal models of systemic bacterial infections.

Role of cytokines

It is well known that cytokines orchestrate non-specific and specific immune reactions. They are broadly categorized as being pro-inflammatory or anti-inflammatory, i.e. they are involved in both the pathogenesis of signs of disease, such as anorexia and fever, and the host defence against the disease (for review, see Oppenheim, 2001). Several pro-inflammatory cytokines, such as IL-1, IL-2, IL-6, IL-8, IL-18, TNFα, interferon-γ (IFN-γ) and ciliary neurotrophic factor (CNTF), have been implicated in LPS anorexia. Each of these cytokines has been shown to inhibit eating after peripheral or central administration (for example, see Plata-Salaman, 1995; Langhans & Hrupka, 1999; Lambert *et al*. 2001; Netea *et al*. 2006) and some of them are known to act synergistically (Yang *et al*. 1994; Sonti *et al*. 1996). The synergies are presumably related to the overlapping effects of the cytokines and to the fact that they act through converging intracellular signalling pathways. Leptin, which is not considered to be a classical cytokine, also affects immune functions and is in many aspects similar to cytokines (Sanchez-Margalet *et al*. 2003). Leptin is also implicated in the feeding-inhibitory effect of LPS (see p. 323).

While genetic ablation of a particular cytokine or its receptor often does not substantially attenuate the anorectic effect of peripheral LPS (for review, see Langhans, 2004), acute pharmacological or immunological antagonism of cytokines appears to be generally more effective (Bluthe *et al*. 1992; Porter *et al*. 1998*a*, 2000; Swiergiel & Dunn, 1999; Laye *et al*. 2000; Harden *et al*. 2006). These seemingly discrepant findings may be related to the redundant and overlapping actions of the cytokines, which could permit unusually extensive developmental compensation. Accordingly, simultaneous interference with several cytokines often has a stronger effect on LPS anorexia than acute blockade of only one cytokine alone; indeed, such compound treatments are at times necessary in order to observe any effect (Swiergiel & Dunn, 1999; Bluthe *et al*. 2000), suggesting that pro-inflammatory cytokines can replace each other to a certain extent in mediating LPS anorexia.

Some data suggest a special role for IFN-γ in LPS anorexia (Arsenijevic *et al*. 2000). IFN-γ is mainly produced in T-cells and natural killer cells (Billiau & Vendenbroeck, 2001), neither of which possesses TLR-4 (Beutler, 2002). Thus, LPS indirectly stimulates IFN-γ production through macrophage-derived IL-12 and IL-18 as well as TNFα (Doherty *et al*. 1992; Billiau & Vendenbroeck, 2001). The main function of IFN-γ is to activate macrophages and EC, partly in synergy with macrophage-derived cytokines (Billiau & Vendenbroeck, 2001). Thus, by enhancing pro-inflammatory cytokine production and

action, IFN-γ may be essential for the full expression of LPS anorexia (Arsenijevic *et al*. 2000). In general, although it is clear that pro-inflammatory cytokines play a prominent role in mediating LPS anorexia, the complex interactions among several cytokines rather than the action(s) of any single cytokine appear to be crucial.

Roles of leptin and ghrelin

Leptin is another possible mediator of LPS anorexia. LPS and pro-inflammatory cytokines increase the expression and production of leptin in adipose tissue (Grunfeld *et al*. 1996; Faggioni *et al*. 1998; Finck *et al*. 1998), and there is a correlation between these increases and the feeding-inhibitory effects of the cytokines (Grunfeld *et al*. 1996). In turn, leptin increases cytokine expression (Dixit *et al*. 2004). Moreover, neutralization of circulating leptin with a leptin antiserum has recently been shown to reverse the feeding-inhibitory effect of LPS (Sachot *et al*. 2004; Harden *et al*. 2006). Moreover, it was found that LPS causes an up-regulation of IL-1β and IL-1 receptor antagonist mRNA in the hypothalamus, and this effect is also attenuated by leptin antiserum (Sachot *et al*. 2004). These results suggest that leptin is a circulating mediator of LPS anorexia, possibly through a hypothalamic IL-1β-dependent mechanism. On the other hand, it has recently been reported (Gayle *et al*. 2006) that an anorectic dose of LPS given intraperitoneally barely increases plasma leptin in male rats despite a reduction in food intake. Studies in animals with genetic defects in the leptin system have also yielded mixed results. When compared with normal control animals LPS administration has a more pronounced feeding-suppressive effect in *ob*/*ob* (leptin-deficient) mice and it causes weaker food-intake inhibition in *db*/*db* (leptin receptor-deficient) mice (Faggioni *et al*. 1997) than in corresponding wild-type mice. Furthermore, a single intraperitoneal LPS injection reduces food intake similarly in lean (*Fa*/*?*) and obese (*fa*/*fa*) Zucker rats (Lugarini *et al*. 2005). High doses of LPS (500 μg/kg or 1·0 mg/kg) also cause a similar initial (day 1) inhibition of feeding in lean and obese Zucker rats, although the recovery of normal food intake is somewhat delayed after the highest dose (1·0 mg/kg) in obese rats. In general, the available data suggest that leptin or functional leptin receptors are not necessary for the feeding-inhibitory effect of LPS, but that leptin nonetheless contributes to LPS anorexia in several ways.

The contribution of leptin to LPS anorexia might explain two seemingly-unrelated phenomena: (1) the attenuated feeding-inhibitory effect of LPS and pro-inflammatory cytokines after food deprivation; (2) the hypersensitivity of female individuals to LPS anorexia. As food deprivation reduces plasma leptin (Boden *et al*. 1996), stimulation of leptin production by LPS in fasted individuals may fail to sufficiently increase circulating leptin for a feeding-inhibitory effect. As females appear to produce more leptin than males in response to LPS (Gayle *et al*. 2006) and are more sensitive to exogenous leptin than males (Clegg *et al*. 2003), leptin could well contribute to the stronger feeding-inhibitory effect of LPS in females compared with males.

Intraperitoneally administered LPS has been reported to substantially decrease circulating ghrelin (Basa *et al*. 2003; Hataya *et al*. 2003; Wang *et al*. 2006). Interestingly, the LPS-induced decrease in plasma ghrelin is prevented by IL-1 receptor antagonist and indomethacin (Wang *et al*. 2006), suggesting that it is mediated by IL-1β and a prostanoid-dependent mechanism. Exogenous ghrelin antagonizes the LPS-induced inhibition of food intake and gastric emptying (Basa *et al*. 2003; Hataya *et al*. 2003; Wang *et al*. 2006). Although it is unclear how LPS and cytokines inhibit gastric ghrelin production, it has been shown that ghrelin potently stimulates feeding (Tschop *et al*. 2000) and LPS inhibits feeding by reducing meal number (Langhans *et al*. 1989), which is at least consistent with an involvement of ghrelin.

Mode of cytokine action

Vagal afferents

Although IL-1β can activate vagal afferents (Niijima, 1996; Kurosawa *et al*. 1997), this mechanism does not appear to be crucial for the feeding-inhibitory effects of LPS and IL-1β. For example, subdiaphragmatic vagotomy has been reported to attenuate some cytokine-induced phenomena (Dantzer *et al*. 2000), including inhibition of instrumental responses to obtain food induced by intraperitoneal LPS or IL-1β in mice (Bret-Dibat *et al*. 1995). However, subdiaphragmatic vagal deafferentation, alone and in combination with celiac-superior mesenteric ganglionectomy, did not alter the anorexia after intraperitoneal injection of LPS or IL-1β in rats (Schwartz *et al*. 1997; Porter *et al*. 1998*b*). Subdiaphragmatic vagal deafferentation is the most selective and specific method available to lesion vagal afferents. These findings therefore show that abdominal vagal and spinal visceral afferents are not necessary for the anorectic effects of these immune stimuli, at least in the rat.

Blood–brain barrier mechanisms

Pro-inflammatory cytokines produced in response to LPS may directly act on the brain to elicit anorexia because they are actively transported across the blood–brain barrier (BBB) (Banks & Kastin, 1996) and also enter the brain where the BBB is 'leaky', i.e. in the circumventricular organs. Several lines of evidence suggest, however, that non-neural cells of the BBB are the most important site of cytokine action in response to LPS (see Fig. 1). BBB EC and perivascular cells such as microglia and macrophages, presumably together with blood monocytes, have emerged as a highly-complex regulatory interface controlling brain-mediated reactions to peripheral challenges (Licinio & Wong, 1997; Turrin & Rivest, 2004). BBB EC and perivascular cells possess cytokine receptors (VanDam *et al*. 1996; Deckert-Schluter *et al*. 1999) as well as TLR (Laflamme & Rivest, 2001). In addition, membrane-bound CD14 is present on BBB EC under basal conditions (Lacroix *et al*. 1998), and a robust increase in CD14 mRNA levels takes place in these cells in response to a single peripheral injection of LPS (Lacroix *et al*. 1998;

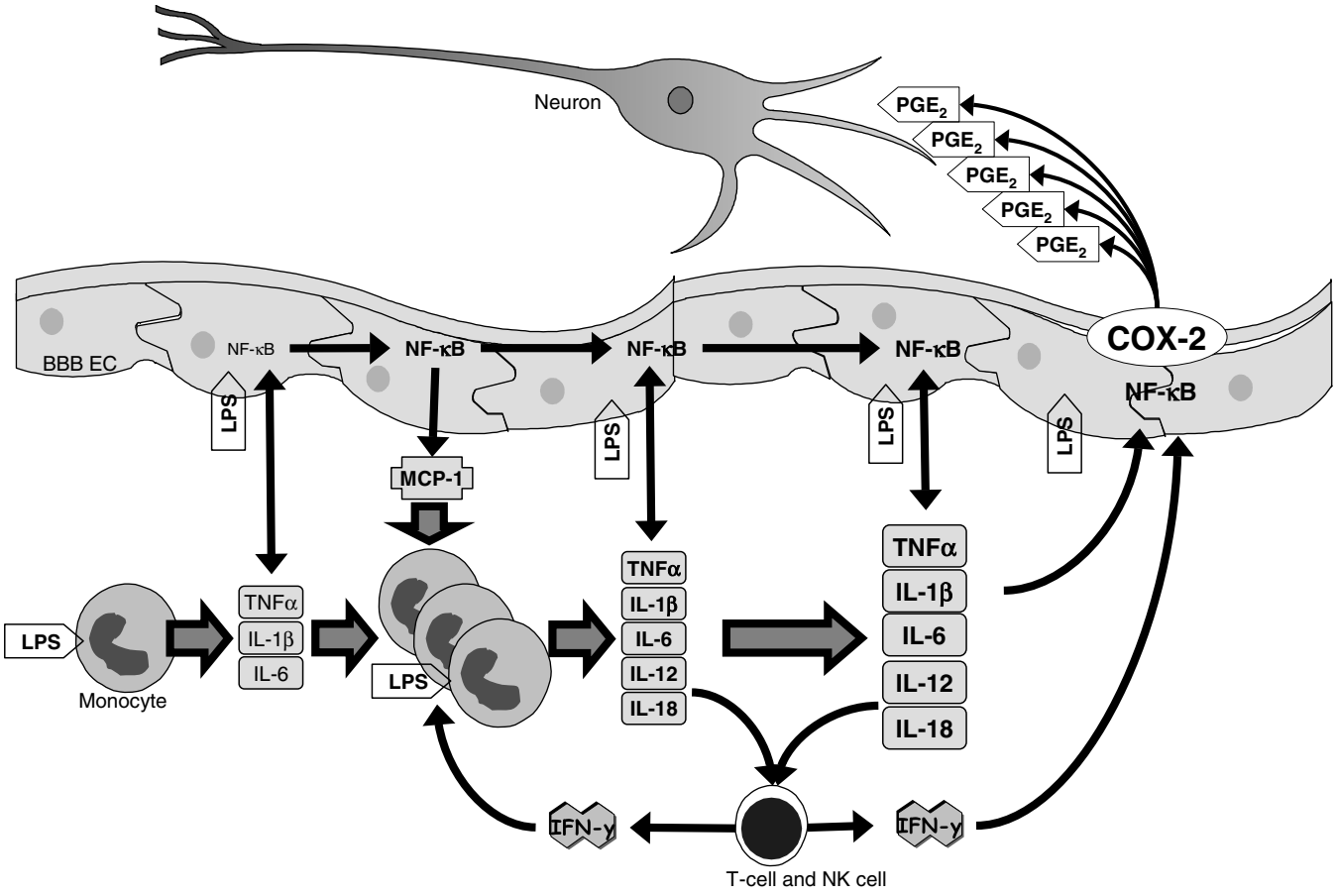

Fig. 1. Schematic diagram of the interactions between monocytes and blood–brain barrier endothelial cells (BBB EC) in the transmission of the lipopolysaccharide (LPS)-induced immune signals causing anorexia. LPS acts on monocytes and BBB EC to stimulate the release of pro-inflammatory cytokines. In response to LPS and cytokines, BBB EC release monocyte chemoattractant protein-1 (MCP-1) which recruits additional monocytes. IL-12 and IL-18 trigger the release of interferon-γ (IFN-γ) from T-cells and natural killer (NK) cells. A major role of IFN-γ is to enhance the production and action of other pro-inflammatory cytokines. The combined action of LPS and cytokines on BBB EC finally activates cyclooxygenase-2 (COX-2) thus stimulating PGE_2 production. PGE_2 modulates neurons involved in control of food intake and energy balance. Perivascular cells (microglia, macrophages) and receptors (CD14, toll-like receptors, cytokine receptors) have been omitted for simplicity. For further details, see p. 323–324.

Rivest, 2003). Accordingly, peripheral administration of LPS or IL-1β leads to a rapid induction of *c-fos* mRNA in all non-neural cells of the BBB (Herkenham *et al*. 1998). Furthermore, LPS and pro-inflammatory cytokines cause activation of the transcription factor NF-κB in BBB EC (Bierhaus *et al*. 2000) and trigger the release of neuromodulators such as prostanoids or NO (Cao *et al*. 1996; Nadeau & Rivest, 1999; Rivest, 1999). Activation of BBB EC and the feeding inhibition induced by IL-1β are both mediated by NF-κB activation. In a recent study (Nadjar *et al*. 2005) intracerebroventricular injection of a specific inhibitor of NF-κB activation was found to block the feeding-inhibitory effect of intraperitoneally-administered IL-1β and dramatically reduce IL-1β-induced *c-fos* expression in various brain regions. These findings strongly support the hypothesis that IL-1β-induced NF-κB activation at the BBB is a crucial step in the transmission of the immune signals mediating anorexia from the periphery to the brain.

BBB EC also produce cytokines (Licinio & Wong, 1997; Bierhaus *et al*. 2000) and show signal transducer and activator of transcription-3 activation in response to LPS (Rummel *et al*. 2005). Furthermore, peripheral immune stimulation by LPS, IL-1β or TNFα triggers a rapid (within 30–90 min) increase in transcription of monocyte chemoattractant protein-1 in BBB EC and all circumventricular organs (Thibeault *et al*. 2001). Only ligands that trigger NF-κB signalling have the ability to increase monocyte chemoattractant protein-1 gene expression. The substantial increase in monocyte chemoattractant protein-1 production attracts monocytes that produce pro-inflammatory cytokines. The interaction of BBB EC and monocytes in response to LPS should thus lead to a substantial increase in local cytokine production and action (Fig. 1), which might explain several failures to relate cytokines in the systemic circulation and LPS anorexia.

An interesting feature of BBB EC is their polarization, with the luminal (blood-facing) and abluminal (brain-facing) cell membranes differing in their lipid, receptor and transporter compositions. Interestingly, constitutive and LPS-induced secretion of pro-inflammatory cytokines produced by BBB EC is polarized in favour of luminal

secretion of these cytokines (Verma *et al*. 2006), whereas other mediators appear to be released abluminally (Fig. 1). Thus, despite the putative role of cytokines in LPS anorexia, it appears unlikely that BBB EC-derived cytokines act as messengers for neurons, suggesting that mediators downstream of pro-inflammatory cytokines, such as prostanoids and/or NO, fulfil this function.

Mediators downstream of cytokines

LPS and cytokines synergistically increase cyclooxygenase 2 mRNA expression in BBB EC and potently stimulate prostanoid, in particular PGE_2, production (DeVries *et al*. 1995; Cao *et al*. 1996; Rivest, 1999). Non-specific cyclooxygenase inhibitors attenuate the anorectic effects of LPS and IL-1β (Langhans *et al*. 1989, 1993). Furthermore, the cyclooxygenase 2 inhibitor NS-398, but not the cyclooxygenase 1 inhibitor resveratrol, attenuated the anorectic effect of intraperitoneal LPS and blocked the concomitant LPS-induced increase in cerebrospinal PGE_2 (Lugarini *et al*. 2002). Interestingly, Pecchi *et al*. (2006) have recently shown a robust up-regulation of microsomal PGE synthase-1 enzyme in the brain in response to intraperitoneally- and intracerebroventricularly administered anorectic doses of IL-1β. Microsomal PGE synthase-1 catalyses the last step of PGE_2 biosynthesis, and its expression is stimulated by pro-inflammatory agents. In addition, IL-1β failed to decrease food intake in microsomal PGE synthase-1(-/-) mice (Pecchi *et al*. 2006), although these animals developed anorexia in response to an injection of PGE_2. Together these results demonstrate that microsomal PGE synthase-1 is essential for IL-1β-induced anorexia. All these findings are consistent with the notion that LPS and cytokines act on BBB EC (Fig. 1) to trigger the production and release of PGE_2, which acts on neurons that are involved in, or are connected to, brain sites involved in food-intake control.

Central nervous system mechanisms

Cytokines

Neurons in various brain areas increase expression of several pro-inflammatory cytokines, their accessory proteins and their receptors in response to peripheral administration of LPS (Gabellec *et al*. 1995; Gayle *et al*. 1997*b*; Turrin *et al*. 2001). While it appears unlikely that centrally produced cytokines are the exclusive mediators of peripheral LPS anorexia (for review, see Langhans, 2004), they may contribute under certain circumstances. Leptin increases hypothalamic IL-1β, central injection of IL-1 receptor antagonist inhibited the hypophagic effect of central or peripheral injection of leptin and IL-1 receptor-knock-out mice did not reduce food intake in response to leptin (Luheshi *et al*. 1999). These data suggest that hypothalamic IL-1β contributes to the feeding-inhibitory effect of leptin. As leptin is a possible mediator of LPS anorexia (see p. 323), central IL-1β might also be involved in peripheral LPS anorexia. More recently, Wisse *et al*. (2006) have shown that the melanocortin antagonist SHU9119 blunts the LPS-mediated increase in hypothalamic IL-1β, but that pharmacological or genetic disruption of IL-1 receptor signalling does not prevent the anorexia induced by the melanocortin agonist MTII. These data question the role of central IL-1β as a major mediator of LPS anorexia because SHU9119 (Huang *et al*. 1999) and genetic lack of the melanocortin-4 receptor (Marks *et al*. 2001) attenuated the feeding-suppressive effect of LPS. Other direct tests of the role of central IL-1β have also yielded inconsistent results; while intracerebroventricular administration of IL-1 receptor antagonist failed to inhibit the feeding-inhibitory effect of intraperitoneal LPS in rats (Bluthe *et al*. 1992), it did attenuate the effect of intraperitoneal LPS in mice (Laye *et al*. 2000). The reason for this discrepancy is unclear.

CNTF, a trophic factor for motor neurons in the ciliary ganglion and spinal cord, has been found to markedly reduce food intake and body weight (see Lambert *et al*. 2001). IL-1β is essential for CNTF production in response to brain injury or trauma (Herx *et al*. 2000), raising the possibility that CNTF may also be a downstream mediator of IL-1β effects on food intake. Some data suggest that CNTF ultimately affects energy balance by reducing the expression and action of neuropeptide Y (Xu *et al*. 1998). A reduction in hypothalamic neuropeptide Y mRNA has also been reported during IL-1β-induced anorexia (Gayle *et al*. 1997*a*), although the decrease in neuropeptide Y expression appears to be too small to account for the substantial reduction in food intake. It is possible, however, that cytokine-induced decreases in neuropeptide Y attenuate the feeding that normally occurs in response to an energy deficit (Inui, 1999). Recently, it has been reported (Steinberg *et al*. 2006) that a potent CNTF analogue and leptin reduce food intake and hypothalamic AMP kinase expression similarly. Numerous reports in the last few years suggest that hypothalamic AMP kinase functions as an energy sensor in the control of energy balance (Small *et al*. 2004).

Serotonin

The increase in *c-fos* expression (i.e. the activation) in medullary and hypothalamic paraventricular neurons that is elicited by LPS or cytokine treatment (Elmquist & Saper, 1996; Ericsson *et al*. 1997; Lacroix & Rivest, 1997) appears to be mediated by PGE_2 (Ericsson *et al*. 1997; Lacroix & Rivest, 1997). This finding is interesting because serotonin (5-HT) and catecholamine cell groups in the midbrain and hindbrain, but not in the paraventricular nucleus, possess PG EP_3 receptors and are activated by PGE_2 (Ericsson *et al*. 1997; Nakamura *et al*. 2001). Serotonergic projections from the midbrain raphe area and the hindbrain to the hypothalamus are particularly interesting candidate pathways for the anorectic effects of LPS and cytokines. First, it has recently been observed (BS Kopf, N Geary, W Langhans and L Asarian, unpublished results) that intraperitoneal LPS increases *c-fos* in large parts of the raphe. Second, it has also been found (see Langhans, 2004) that microinjection of a cyclooxygenase 2 inhibitor into the dorsal raphe nucleus markedly reduces anorexia following intraperitoneal LPS, and that microinjection of PGE_2 into the same area decreases food intake. The dorsal

raphe nucleus also contains IL-1 receptors (Cunningham *et al*. 1992), and central as well as peripheral administration of IL-1β and TNFα increased serotonergic activity in this area (Clement *et al*. 1997). 5-HT potently inhibits eating, apparently mainly through the 5-HT_{1B} and/or 5-HT_{2C} receptors (Simansky, 1995; Nonogaki *et al*. 1998). Pretreatment with a highly-specific 5-HT_{2C} receptor antagonist blocked the anorexia induced by both peripheral and central injection of LPS or IL-1β in rats (von Meyenburg *et al*. 2003*a*,*b*). Furthermore, administration of the 5-HT_{1A} autoreceptor agonist 8-hydroxy-2-di-n-propylamino-tetralin directly into the dorsal raphe nucleus blocked the feeding-inhibitory effect of peripheral LPS and IL-1β (von Meyenburg *et al*. 2003*a*,*b*), whereas pharmacological antagonism of other 5-HT receptors (5-HT_{1B}, 5-HT_{2A}, 5-HT_3) did not. Pharmacological 5HT_{2C} antagonism also attenuated the feeding-inhibitory effect of intraperitoneal LPS in mice, although LPS did not reduce food intake in 5-HT_{2C}-knock-out mice (Asarian *et al*. 2007). In addition, some pharmacological data in mice (Swiergiel & Dunn, 2000) suggest that the involvement of central 5-HT neurons in LPS and cytokine-induced anorexia is situationally variable. In summary, therefore, although several findings implicate the 5-HT neurons in the median raphe nucleus and 5-HT_{2C} receptors in the hypothalamus in LPS anorexia, it is not yet clear whether this mechanism plays a necessary role, at least in mice. Finally, emerging evidence indicates that 5-HT modulates the release of endogenous agonists and antagonists of brain melanocortin receptors, which are crucial for the central control of energy balance (Heisler *et al*. 2002, 2006).

Neuropeptides

LPS increases the number of glucagon-like peptide-1 neurons in the nucleus of the solitary tract that express *c-fos* (Rinaman 1999), and both 3rd-intracerebroventricular and 4th-intracerebroventricular administration of the glucagon-like peptide-1 receptor antagonist exendin-(9–39) attenuated the anorectic response to intraperitoneal LPS in rats (Comer & Rinaman 2000; Grill *et al*. 2004). These findings have recently been extended by Grill *et al*. (2004) to show that 3rd-intracerebroventricular administration of exendin is ineffective when the caudal flow of cerebrospinal fluid is blocked by occlusion of the cerebral aqueduct, which suggests that LPS anorexia is mediated in part by release of glucagon-like peptide-1 within the caudal brain stem.

Recent findings (Becskei *et al*. 2006) suggest that peripheral LPS reduces *c-fos* expression in the lateral hypothalamic area and decreases the number of lateral hypothalamic area neurons expressing orexin-A protein in mice deprived of food for 12 h. As orexin-A has a potent orexigenic effect (Rodgers *et al*. 2002), this finding raises the possibility that a decrease in orexin-A expression contributes to LPS anorexia. Since orexin-A is mainly implicated in arousal (Rodgers *et al*. 2002), the inhibitory effect of LPS on orexin-A protein-expressing neurons might also be involved in LPS-induced lethargy and inactivity.

Peripheral injection of IL-1β increased hypothalamic corticotrophin-releasing factor mRNA (Suda *et al*. 1990), and IL-1β-induced anorexia was attenuated by 3rd-intracerebroventricular administration of a corticotrophin-releasing factor antagonist (Uehara *et al*. 1989), suggesting that hypothalamic corticotrophin-releasing factor is involved in IL-1β-induced anorexia. Prostanoids mediate the effect of IL-1β on hypothalamic corticotrophin-releasing factor release (Watanabe *et al*. 1990), suggesting a link between the putative role of PGE_2 (Langhans *et al*. 1993; Lugarini *et al*. 2002) and corticotrophin-releasing factor (Uehara *et al*. 1989) in the anorectic effects of LPS and IL-1β.

Finally, LPS stimulates the release of α-melanocyte-stimulating hormone (Catania *et al*. 1995), which antagonizes acute-phase reactions at various levels (cytokine production, cytokine action; Lipton & Catania, 1998). α-Melanocyte-stimulating hormone binds to central melanocortin receptors (MC*n*-R; MC3-R and MC4-R), and central administration of MC4-R agonists inhibits food intake, increases energy expenditure and reduces body weight (see Tritos & Maratos-Flier, 1999). In turn, deficiency of the MC4-R is associated with increases in food intake and body weight (Fan *et al*. 1997). Intracerebroventricular administration of α-melanocyte-stimulating hormone enhanced, and intracerebroventricular administration of the MC3-R and MC4-R antagonist SHU9119 attenuated, intraperitoneal LPS anorexia in rats (Fan *et al*. 1997; Huang *et al*. 1999). More recently, the anorexia induced by intraperitoneal LPS and cytokines has also been shown to be attenuated by the endogenous MC3-R and MC4-R antagonist Agouti-related peptide and in MC4-R-knock-out mice but not in MC3-R-knock-out mice (Marks *et al*. 2003). These results specifically implicate the central MC4-R in LPS and cytokine-induced anorexia. Given the putative role of 5-HT in the anorectic effects of LPS and IL-1β (see p. 325), it is interesting to note that the melanocortin system is a downstream target of serotonergic neurons (Heisler *et al*. 2002, 2006).

Concluding remarks

In summary, the signalling pathways of LPS anorexia ultimately converge on well-known neurotransmitter and neuropeptide systems that control food intake and energy balance. Assuming that the overlap between the mechanisms of LPS anorexia and physiological satiety generalizes to the anorexia during other illnesses, the data discussed here are consistent with the view that illness-related anorexia, like other disease mechanisms, does not represent a completely new physiological adaptation, but rather results from modulation of normal homeostatic processes that operate in healthy individuals.

Finally, it is important to understand the mechanisms of illness anorexia in order to design well-targeted therapeutic approaches for this clinically-important problem. Despite considerable progress towards an understanding of these mechanisms over the last few years, however, further studies are necessary before effective and specific therapies for the various forms of illness anorexia can be proposed.

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